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[redacted]

CONSENT TO TAKE PART IN A RESEARCH STUDY

TITLE OF STUDY:
A Phase I Study to Evaluate the Safety of Trigriluzole (FC-4157/BHV-4157) in Combination with PD-1 Blocking Antibodies

Principal Investigator: [redacted]

This consent form is part of an informed consent process for a research study and it will provide information that will help you to decide whether you wish to volunteer for this research study. It will help you to understand what the study is about and what will happen in the course of the study.

If you have questions at any time during the research study, you should feel free to ask them and should expect to be given answers that you completely understand.

After all of your questions have been answered, if you still wish to take part in the study, you will be asked to sign this informed consent form.

The study doctor (the principal investigator) or another member of the study team will also be asked to sign this informed consent form. You will be given a copy of the signed consent form to keep.

You are not giving up any of your legal rights by volunteering for this research study or by signing this consent form.

Sponsor of the study:
[redacted]

The costs that are usually covered include things such as research laboratory tests required by the study, and the costs of collecting all of the information required by the study.

Why is this study being done?
The purpose if this study is to find if the investigational drug trigriluzole (also called FC-4157 or BHV-

[redacted]
Version date: 12/04/2018

NCI [redacted] Cancer Center

Expiration Date: 4/3/2020

4157) is safe to use in combination with the FDA-approved anti-cancer drugs called nivolumab or pembrolizumab, which are both in the class of drugs called anti-PD-1 antibodies. This study will test increasing doses of trigriluzole given with one of the anti-PD-1 antibodies at a standard dose.

Trigriluzole, the investigational drug is a pro-drug (new formulation) of a drug called riluzole, which is FDA-approved to treat a neurologic disease called amyotrophic lateral sclerosis. An investigational drug is one that is not approved by the FDA to treat your disease. A '**prodrug**' is not an active drug but it is converted into an active drug in the body; which means trigriluzole when taken by mouth readily converts into riluzole. In laboratory studies, riluzole slows the growth of cancer cells, and decreases certain immune suppressive cells in the tumor, which may make tumors more susceptible to treatment with PD-1 antibodies.

PD-1 inhibitors help the body's immune system work against tumor cells. Typically, the human body's immune system recognizes abnormal cells in the body and destroys them. Cancer cells frequently create proteins on the cell surface (PD-L1) that act as signals to turn off this part of the immune system, not allowing them to interact with the PD-1 protein that is expressed on the immune cells. Nivolumab is a PD-1 antibody (a type of human protein) that is approved by the FDA for the treatment of certain types of cancers like melanoma, some forms of lung cancer, kidney cancer, squamous cell carcinoma of the head and neck, bladder cancer and Hodgkin lymphoma. Pembrolizumab is also a PD-1 antibody and has been approved by the FDA to treat melanoma, some forms of lung cancer, squamous cell carcinoma of head and neck, and Hodgkin lymphoma. Both of the PD-1 inhibitors used in this study (nivolumab and pembrolizumab) are also under investigation for many other types of cancers in various clinical trials in combinations with various other agents.

The safety and how well this drug combination is tolerated will be determined based on vital signs, physical exams, laboratory tests, imaging and quality of life questionnaire and any problems you might experience during the study.

The other purposes of this study are to determine:

- best dose of trigriluzole
- effect of study drugs on the growth of your cancer
- how immune cells in your blood and tumor are affected by study treatment
- how proteins in your blood and tumor are affected by study treatment

There are two parts to this study:
Part 1: To find the best dose of trigriluzole in combination with nivolumab
Part 2: To find the best dose of trigriluzole in combination with pembrolizumab

You will be explained in detail about what will happen in study. If you have any questions or if you don't understand anything, ask the doctor or the study staff to explain before you sign this form.

Why have you been asked to take part in this study?
You are being asked to participate in this research study because you have a cancer that is metastatic (has spread to other areas of the body) or cannot be removed by surgery and your doctors believe that there is

[redacted]

reasonable expectation of benefit if you took nivolumab or pembrolizumab.

Who may take part in this study? And who may not?
You may be included in this study if:

- You are more than 18 years of age
- You are diagnosed with advanced stage cancer that is not responding to other treatment or no other standard treatment is available.

You may not be included in this study if:

- Your blood tests are very abnormal
- You have a serious infection
- You are taking steroids

The study doctor and/or research team will also ask you other questions about your medical history in order to make sure you qualify to be in this study.

How long will the study take and how many subjects will participate?
Your study treatment is expected to last until your cancer gets worse or until you are no longer receiving benefits from the treatment maximum up to 109 weeks. You may stop taking part in study at any time for any reason.

A total of 12 - 27 subjects will be enrolled study wide at [redacted]

What will you be asked to do if you take part in this research study?
Before you begin study treatment:
You will have some exams, tests and procedures to find out if you can take part in this study. Most of the exams, tests, and procedures you will have are part of the usual approach for your cancer. However, your doctor will do some extra testing as part of the study. The testing that you will need to have if you take part in this study is discussed below. If some of these have been done recently they may not need to be repeated, this will be up to the study doctor.

- A medical history including questions about your health, current medications, and any allergies
- A physical exam. The research doctor or another research healthcare professional will complete a physical assessment, including blood pressure, pulse, rate of breathing, temperature, and height and weight.
- An assessment of your tumor by scan. Scans may include:
    - Computed tomography (CT), a scan that uses x-rays to look at one part of your body. It may be done with or without contrast. Contrast means that dye is injected into your vein to increase the differences between normal and abnormal tissue. CT scans are preferred, but PET/CT scans may be done instead of CT scans if you have kidney problems or if your doctor thinks PET/CT is preferable for measuring your tumor.
        - Position emission tomography (PET), a scan that uses a small amount of radioactive glucose (sugar) injected into your vein to make a detailed, computerized image of different parts of the body where the sugar is taken up.

  - Magnetic resonance imaging (MRI), imaging that uses a strong magnetic field to look at your brain, if needed.
- Blood tests:
  - Approximately 2 teaspoons (10 mL) for routine testing, such as, a complete blood count, kidney and liver function tests to ensure that it is safe to administer any of the drugs included in this study
  - Approximately 1 teaspoon (5 mL) for blood clotting tests
  - Approximately 1 teaspoon (5 mL) for thyroid function testing
- Pregnancy test, if you are a woman of child-bearing potential.
- Electrocardiogram (also known as an ECG or EKG). This is a painless paper tracing of your hearts normal electrical activity
- If there is a tumor that can be easily removed by a biopsy (a sample of the tumor) in the office setting, for research purposes. You may choose not to have this procedure if you do not want to (optional). You may still be enrolled in this study if you say no. This procedure will be done at no additional cost to you.
- A sample of your tumor from a previous biopsy will be obtained when available.

If you do not meet the eligibility requirements, you cannot take part in this study. The study doctor will inform you of other options that are available to you.

If the tests, exams, procedures show that you can be in the study and you are agreeable to continue, then you will be enrolled to the study.

<u>While on study treatment:</u>
This is a dose escalation trial, which means the dose of trigriluzole will increase as more patients are enrolled. This study will determine the dose of study drug trigriluzole that can be safely administered with the PD-1 blocking drugs nivolumab and pembrolizumab and the effect on cancer. As the study progresses, additional patients who enroll will receive higher doses of trigriluzole. You will take trigriluzole tablets by mouth and the other drugs will be administered by vein (IV) by a nurse at the cancer center.

This study is "open label," which means that both you and the study doctor will know your study drug assignment. Although different dose levels of trigriluzole will be tested in combination with nivolumab, the dose level of nivolumab or pembrolizumab will be the same. The dose level of trigriluzole that you will receive will be assigned to you upon enrollment to the study.

Part I: The study will first test the safety of trigriluzole and nivolumab, which is given once every 2 weeks. Each dose group gets a different dose of trigriluzole to decide the safe dose of trigriluzole. First 3 patients will be enrolled in the lowest dose group. After that group 2 will open for treatment. If all the patients in this group tolerate the drug, next 3 patients will be enrolled in group 3. If all the patients in this group tolerate the drug, next 3 patients will be enrolled in group 4. The four groups are as follows:

- **Group 1:** 140 mg of trigriluzole by mouth every morning
- **Group 2:** 140 mg of trigriluzole by mouth twice a day

- [redacted]iluzole by mouth every morning and 280 mg every evening
- **Group 4:** 280 mg of trigriluzole by mouth twice a day

You will take the trigriluzole by itself for 14 days prior to receiving your first dose of nivolumab. Then you will receive 240 mg of nivolumab IV every 2 weeks and continue to take trigriluzole by mouth.

Part 2: Once the maximum dose that can be safely given to patients is identified, then in next group of patients will be treated with that dose of trigriluzole + pembrolizumab.

You will take the trigriluzole for 14 days prior to receiving your first dose of pembrolizumab. Then you will receive 200 mg of pembrolizumab IV every 3 weeks and continue to take trigriluzole by mouth.

During the treatment period, you will need the following examinations, tests, and procedures described below. Some of these exams, tests, and procedures are part of your regular medical care (standard of care).

- Physical Exams: You will have regular physical exams, including measuring your weight. You will be asked questions about your general health and specific questions about any problems that you might be having and any medications you may be taking. Please tell your doctor about any medical treatments that you will have to get during the study (such as scheduled surgery).
- Blood Tests:
  - Every 2-3 weeks: For the first 8 weeks, approximately 2 teaspoons (10 mL) for routine testing, such as, a complete blood count, kidney, liver, and thyroid tests to ensure that it is safe to administer any of the drugs included in this study.
  - After the first 8 weeks, these tests will be performed every 6 weeks.
  - Research blood collection for drug levels: Approximately 1 teaspoons (5 mL) of blood will be collected on the first day of treatment (Week -2) at 3 times (prior to dose, 2 hours after dose, and 4 hours after dose). In addition, approximately 1 teaspoons (5 mL) of blood will be collected on at Week 1 and Week 6.
  - Research blood collection for biologic studies: Approximately 1 teaspoons (5 mL) of blood will be collected on the first day of treatment (Week -2). In addition, approximately 1 teaspoons (5 mL) of blood will be collected on at Week 1, Week 6, and Week 12.
- Pregnancy test, if you are a woman of child-bearing potential.
- Assessment of your cancer: by CT scan. These assessments will be performed at Week 7 and Week 13 and then every 12 weeks. If your cancer is found to be improving, you will be asked to repeat the CT scans in 4-12 weeks to confirm the response.
- Biopsies (a sample of the tumor): If there is a tumor that can be easily sampled by a biopsy in the office setting, a tumor biopsy will be performed at Week 1 and again at Week 6 to determine how the tumor and the immune cells in the tumor are responding to the treatment (biopsies optional but strongly encouraged). This procedure will be done at no additional cost to you.

Your doctor will stop study treatment if any of the following occur:

- You have completed study treatment as planned
- Your doctor decides that your disease is worse (disease progression)

[redacted]

[redacted]

[redacted]

- You develop unacceptable side effects
- You become pregnant or are unwilling to use appropriate birth control techniques
- The study doctor determines that it is not in your best interest to continue the study treatment
- New information becomes available
- The study is stopped by the sponsor, [redacted], the IRB, or FDA
- You choose to stop study treatment

After you have completed study treatment:

After all study treatment has stopped, your doctor will ask you to return to the clinic for an end of treatment visit, which will be approximately 12 weeks after your last dose of study drug. The following assessments will be done at these visits:

- You will be asked to report any symptoms and health problems you have and any new medications you have started.
- You will have a complete physical examination, with your physician or physician's assistant, including measurement of your vital signs (breathing rate, blood pressure, temperature, and heart rate), height, and weight.
- Evaluation of your ability to carry out daily activities.
- You will have blood tests:
    - Approximately 2 teaspoons (10 mL) for routine testing, such as, a complete blood count, kidney, and liver function tests.

If you have any ongoing side effect at the time you complete the study or your doctor discontinues you from the study, the study doctor will continue to follow your condition until the side effect resolves or becomes stable.

Long-Term Follow-Up

If your disease worsens or you stop study treatment, the study staff will contact you approximately every 12 weeks after your last visit to check on your health status. If they are not able to reach you, they may use a public information source (like county records) to obtain information about your survival status only, which will be reported as part of the data for the study.

What are the risks and/or discomforts you might experience if you take part in this study?

Treatments for cancer often have side effects, including some that are life-threatening. There is the possibility of death occurring as a result of this treatment and its side effects. There may be additional unknown risks.

If you experience severe side effects associated with the study drug, your doctor may prescribe medications to treat the side effect(s), future treatments may be delayed, or treatment may be stopped permanently. Any significant new findings that develop during the course of the research and may relate to your willingness to continue participation will be provided to you.

The effects of trigriluzole in humans are not yet known. Because the drug is converted to its active form as riluzole in the human body, we anticipate that this drug will have similar adverse effects as riluzole.

Some of the common side effects of riluzole are as follows:

- Nausea and vomiting
- Dizziness
- Diarrhea
- Abdominal pain
- Vertigo (feeling like the room is spinning)
- Skin sensation such as burning , pricking, itching or tingling sensation with no apparent physical cause (Circumoral paresthesia)
- Sleepiness (somnolence)
- Decreased lung functions
- Abnormal physical weakness or lack of energy (Asthenia)

Other less common side effects are:

- Effect on the liver leading to increase in levels of liver function blood tests.

Rare side effects associated with riluzole include

- Low hemoglobin (Anemia) and decrease in white blood cells (Neutropenia)
- Rarely patients treated with riluzole have developed interstitial lung disease (thickening of lung tissue which limits oxygen passing through) or hypersensitivity pneumonitis (inflammation of the lungs).

Risks and adverse effects associated with Nivolumab:
Nivolumab may cause one or more of the side effects listed below. This information is based on data from cancer subjects in other clinical trials with nivolumab. In addition, there may be side effects that are not yet known that may occur. You should tell your doctor or nurse right away about any possible side effects you experience.

Very common side effects of nivolumab are: [More than 1/10]

- Fatigue
- Rash

Common side effects of nivolumab include: [More than 1/100 to less than 1/10]

- Abdominal pain
- Alkaline phosphatase increased: lab test result associated with liver or bone abnormalities
- ALT increased: lab test result associated with abnormal liver function
- Amylase increased: lab test result associated with pancreas inflammation
- AST increased: lab test result associated with abnormal liver function
- Chills
- Cough
- Creatinine increased: lab test result associated with decreased kidney function
- Decreased appetite
- Diarrhea
- Dry mouth

- Dry skin
- Fever
- Headache
- Lipase increased: lab test result associated with pancreas inflammation
- Inflammation of the colon
- Inflammation of the mouth
- Infusion related reaction
- Itching
- Joint pain or stiffness
- Loss of color (pigment) from areas of skin
- Lung inflammation (pneumonitis - see details below)
- Musculoskeletal pain
- Nausea
- Shortness of breath
- Swelling, including face, arms, and legs
- Thyroid gland function decreased
- Thyroid gland function increased
- Thyroid stimulating hormone increased: lab test result associated with abnormal thyroid function
- Tingling, burning, numbness or weakness, possibly in arms, legs, hands and feet
- Vomiting
- Constipation

Uncommon side effects of nivolumab include: [More than 1/1,000 to less than 1/100]

- Adrenal gland function decreased
- Allergic reaction
- Bilirubin (liver function blood test) increased
- Bronchitis
- Cranial nerve disorder (problems with the nerves in the face and neck)
- Diabetes
- Dizziness
- Dry eye
- Hair loss
- Heart rate increased
- Heart rhythm abnormal
- High blood pressure
- Hives
- Increased blood sugar
- Inflammation of the eye
- Inflammation of the heart
- Inflammation of the kidney
- Inflammation of the pancreas
- Inflammation of the pituitary gland
- Inflammation of the stomach
- Inflammation of the thyroid gland

- Liver inflammation
- Low blood pressure
- Pituitary gland function decreased
- Psoriasis: characterized by patches of abnormal, scaly skin
- Redness of the skin
- Renal failure
- Respiratory failure
- Sodium levels in blood low
- Upper respiratory tract infection
- Vertigo
- Vision blurred

Rare side effects of nivolumab include: [More than 1/10,000 to less than 1/1,000]

- Anaphylactic reaction (severe allergic reaction)
- Damage to the protective covering of the nerves in the brain and spinal cord
- Diabetes complications resulting in excess blood acids and diabetic coma
- Erythema multiforme: skin inflammatory reaction
- Guillain-Barre syndrome, an autoimmune disorder associated with progressive muscle weakness or paralysis
- Inflammation of blood vessels
- Inflammation of the brain, potentially life-threatening or fatal
- Lung infiltrates, associated with infection or inflammation
- Muscle inflammation, or inflammation of the heart muscle
- Myasthenic syndrome (neurologic syndrome characterized by muscle weakness) including myasthenia gravis, a nerve disease that may cause weakness of eye, face, breathing, and swallowing muscles.
- Polymyalgia rheumatica, an inflammatory disorder causing muscle pain and stiffness
- Rhabdomyolysis: muscle fiber released into the blood stream which could damage your kidneys
- Rosacea: acne-like skin condition resulting in redness of face
- Sarcoidosis, a disease involving abnormal collections of inflammatory cells (granulomas) in organs such as lungs, skin, and lymph nodes
- Stevens Johnson syndrome: inflammatory disorder of skin and mucous membranes, resulting in blistering and shedding of skin
- Toxic epidermal necrolysis: a potentially fatal disease characterized by blistering and peeling of the top layer of skin resembling a severe burn
- Histiocytic necrotizing lymphadenitis or Kikuchi lymphadenitis: disorder of the lymph nodes which causes the lymph nodes to become enlarged, inflamed and painful, commonly affecting lymph nodes of the neck and possibly associated with fever or muscle and joint pains.

Lung Inflammation (pneumonitis): It is possible that nivolumab may cause inflammation of the tissues of the lung. This adverse effect has been reported infrequently in patients treated with nivolumab. While many patients with x-ray or CT abnormalities have not developed any symptoms, some patients have developed mild to severe symptoms and in rare cases, death has occurred as a result of their lung inflammation. Signs and symptoms of lung inflammation may include difficulty

breathing, pain or discomfort while breathing, chest pain, cough, shortness of breath, increased rate of breathing, fever, low blood oxygen levels, or fatigue.
Your study doctor and nurse will watch you closely for changes in your ability to breathe and for other signs or symptoms that might show you are developing this type of lung inflammation and will perform regular tests including physical exams, measurement of oxygen levels through non-invasive testing (i.e., pulse oximeter), blood tests, chest x-rays and/or CT scans.

Please inform your study doctor or nurse AT ONCE if you experience any of the following:

- Any new or increased shortness of breath;
- Any new or increased chest pain;
- Any new or increased pain/difficulty while breathing;
- Any new or increased cough or any significant change in your type of cough; for example any new or increased mucous or blood in your cough;
- Any change in the amount of oxygen you require;
- Any fever, fatigue, or other symptoms that occur at the same time as any changes to your breathing or other lung symptoms.

If you start to develop symptoms, your study doctor will ask you to return to the clinic for additional tests, which could include a physical exam, measurement of oxygen levels, blood tests, chest x-rays, and/or CT scans. You will be monitored very closely for changes in your overall lung symptoms, monitoring may require hospitalization. You may require specific treatment in order to control pneumonitis. You may also be seen by a special doctor called a pulmonologist, who has special training to be an expert in how your lungs work.

Prolonged treatment with medicines that suppress inflammation, sometimes needed to manage the side effects of nivolumab treatment, may lower your body's ability to fight off certain infections (i.e., opportunistic infections). These infections may require treatment with antibiotic or antifungal medications and may be fatal.

Risks and adverse effects associated with Pembrolizumab/KEYTRUDA
The most common treatment related side effects are shown below. Some are discussed in greater detail under auto-immune side effects.

Very common side effects seen in more than 20% of patients treated with pembrolizumab/KEYTRUDA® include the following:

- Itching of the skin
- Loose or watery stools
- Cough

Common seen in more than 10% to less than 20% of patients treated with pembrolizumab/KEYTRUDA® include the following:

- Joint pain

- Fever
- Back pain
- Rash

Common side effects seen in more than 1% to less than 10% of patients treated with pembrolizumab/KEYTRUDA® include the following:

- Not enough thyroid hormone so you may feel tired, gain weight, feel cold, have infrequent or hard stools
- Too much thyroid hormone so you may feel anxious, angry, can't sleep, weak, tremble, sweat, tired, have loose and watery stools
- Inflammation of the skin so you may have peeling of the skin, itching, skin redness
- Low level of salt in the blood that may cause you to feel tired, confused, headache, muscle cramps or upset stomach
- Inflammation of the lungs so you may feel short of breath and cough. Rarely this may lead to death
- Inflammation of the bowels/gut that can cause stomach pain with loose or watery stools
- Pain in your belly
- Loss of skin color
- Dizziness or fainting (low blood pressure), flushing, rash, fever, shortness of breath or sick to your stomach at the time of receiving your infusion (IV) or just after, or pain at the site of infusion

Common Serious side effects seen in 1% to 4% of patients treated with pembrolizumab/KEYTRUDA® include the following:

- Inflammation of the lungs so you may feel short of breath and cough. Rarely this may lead to death
- Inflammation of the bowels/gut that can cause stomach pain with loose or watery stools, or stools that are black, tarry, sticky or have blood or mucus
- Fever

Immune-mediated serious side effects seen in less than 1% of patients treated with pembrolizumab/KEYTRUDA® include the following:

- Inflammation of the skin so you may have widespread peeling of the skin, itching, and skin redness. More severe skin reactions may involve the inside of your mouth, the surface of your eye and genital areas, and/or may cause the top layer of your skin to peel from all over your body which can cause severe infection. Rarely these reactions lead to death.
- Inflammation of the liver so you may feel not hungry, tired, mild fever, muscle or joint aches, upset stomach and vomiting, stomach pain, bleeding and bruising more easily than normal, yellow eyes and skin, dark urine.
- Inflammation of the pituitary gland (a gland in the head), which may cause headaches, upset stomach, changes in behavior, double vision, few to no menstrual cycles, weakness, vomiting and dizziness or fainting.

- Adrenal glands (glands that control blood pressure and stress response) may not make enough hormone causing tiredness, weight loss, muscle weakness, feeling faint, joint, muscle and abdominal aches, nausea, vomiting, loose or watery stools, fever, salt craving, rapid heart rate, and sometimes darkening of the skin like a suntan.
- Too much thyroid hormone so you may feel anxious, angry, can't sleep, weak, tremble, increased sweating, weight loss, hair loss, tired, have loose and watery stools.
- Not enough thyroid hormone so you may feel tired, gain weight, feel cold, have infrequent or hard bowel movements.
- Inflammation of the kidney so you may pass less urine, have cloudy urine, see blood in your urine, swelling and low back pain.
- Inflammation of the muscles so you may feel weak or pain in the muscles.
- Inflammation of the pancreas (a gland in your abdomen that controls sugar levels) so you may have severe upper abdominal pain that may move to the back, sick to your stomach, and vomiting that gets worse when you eat.
- Inflammation of the eye so you may have redness of the eye, blurred vision, sensitive to light, have eye pain, see floaters or have headaches
- Too much sugar in your blood (diabetes) so you may feel thirsty, and are likely to need regular insulin shots.
- Inflammation of the nerves that may cause pain, weakness or tingling in the hand and feet, and may spread to the legs, arms and upper body leading to severe muscle weakness and possibly temporary paralysis.
- Inflammation of the middle layer of your heart wall (myocarditis) that may cause your heart to have difficulty pumping blood throughout your body, which can cause chest pain, shortness of breath and swelling of the legs. You may experience a fast or irregular heartbeat that may cause dizziness or fainting. Sometimes this condition can lead to death.

Additional serious side effects seen in less than 1.0% of patients treated with pembrolizumab/KEYTRUDA® include the following:

- Dizziness or fainting (low blood pressure), flushing, rash, fever, shortness of breath or sick to your stomach at the time of receiving your infusion (IV) or just after, or pain at the site of infusion.

In addition to the above, the following side effect(s) have been seen in patients on pembrolizumab, but are still being evaluated to determine if they are related to the drug:

- A condition where you will feel weakness and fatigue of your hip and thigh muscles and an aching back caused by your body's immune system attacking your healthy cells and tissues.

Risks Related to Reproductive health/sexual activity
You should not become pregnant or father a baby while on this study because the drugs in this study can

affect an unborn baby. Researchers have not studied the effect of the study drug trigriluzole on human sperm and eggs. Trigriluzole has not yet been studies in fertility and fetal development studies. Riluzole has been known to cause fetal death and deformity, which is the active form of trigriluzole. Nivolumab and pembrolizumab are likely to cause harm to the developing fetus. Therefore, both men and women should not attempt pregnancy and women should not be pregnant or breast-feeding while taking part in this study and for at least 5 months after your last dose of the study drugs. It is important you understand that you need to use birth control for as long as you are receiving treatment on this study and for 5 months after completion of all treatment to prevent pregnancy or fathering a child.

If sexually active, both men and women should use an effective method of birth control while taking the study drug. Barrier contraceptives (condoms or diaphragm) with spermicide, intrauterine devices (IUDs), hormonal contraceptives, oral contraceptive pills, surgical sterilization, and complete abstinence are examples of effective methods. Only methods that use condoms provide reasonable/true protection against sexually transmitted diseases. If you or your partner becomes pregnant while taking the study drug, you must tell your study nurse/doctor immediately. You may have to stop the study drug. Your doctor will discuss other treatment options with you if you stop the study drug.

A woman should not breast-feed a baby while in this study because the PD-1 antibodies may enter the breast milk and possibly harm the child.

If you are a woman capable of bearing children, you will have a pregnancy test before you can participate in this study. If at any time during the study or within 5 months after your last dose of the study drug PD-1 antibody you suspect that you have become pregnant, please notify the study doctor immediately.

Male participants should immediately inform the study doctor if your partner becomes pregnant during the study, within 5 months after your last dose of the PD-1 antibody.

There is a small chance that treatment in the study may make you unable to have children in the future. You can ask your doctor for information about pre-treatment or post-treatment reproductive or fertility options prior to agreeing to participate in the study.

Risks associated with research biopsies

There are some risks associated with a biopsy. Biopsies are optional but strongly encouraged to meet the scientific objectives of this study.

- Pain and discomfort at the biopsy site
- Minor bleeding at the biopsy site
- Tenderness at the biopsy site
- Scarring at the biopsy site
- Rarely, an infection at the biopsy site.

Can you take other medicines while on this study?

You doctor will review your medication list at the start of the study and at each visit.

You are asked to avoid (limit as much as you can) caffeine and smoking tobacco due to possible drug-drug interactions. Please limit caffeine to 1 caffeinated beverage per day or less and limit smoking to less than one pack of cigarettes per week.

You should not take any over-the-counter medicines, herbal products, vitamins or food supplements while taking part in this study, unless you tell the study doctor and get permission from the study doctor to go on taking these medicines. You will follow the instructions of the study doctor about the use of any of these products. You should also tell the study doctor about all medicines that other doctors may have prescribed for you to take.

Are there any benefits for you if you choose to take part in this research study?
There may or may not be direct medical benefit to you from taking part in this study. For patients with the types of cancer that routinely treated with the PD-1 antibodies (including melanoma, kidney cancer, lung cancer, head and neck cancer, and Hodgkin's lymphoma), you may receive a direct medical benefit related to the PD-1 antibody. It is not known if the trigriluzole is effective anti-cancer medication.

It is hoped that the information learned from this study will benefit other patients with cancers in the future.

What are your alternatives if you don't want to take part in this study?
Talk to your doctor about your choices before you decide if you will take part in this study. Depending on your type of cancer, standard treatments may include other immunotherapy, chemotherapy, targeted therapy, or best supportive care/hospice. There also may be other clinical trials available to you.

The most common cancer types expected to be in this study are lung cancer, lymphoma, kidney cancer, and melanoma. For lung cancer and lymphoma, most patients are treated with chemotherapy. For kidney cancer, most patients are treated with targeted treatments, which can be given IV or as pills. For melanoma, immunotherapy and sometimes targeted drugs are used.

You are under no obligation to take part in this research study. If you decide that you do not wish to take part in this study, you are free to leave the study at any time.

How will you know if new information is learned that may affect whether you are willing to stay in this research study?
During the course of the study, you will be updated about any new information that may affect whether you are willing to go on taking part in the study. If new information is learned that may affect you after the study or your follow-up is completed, you will be contacted.

Will there be any cost to you to take part in this study?
You and/or your insurance company will be billed for the costs of your treatment that are considered standard of care (for example, doctor/ Advanced Practice Nurse (APN) visits, nursing care to administer the treatments, routine lab tests, restaging scans, etc.) as you would have received most of these services even if you were not participating in this study. You will be responsible for any co-payments due for office visits, co-insurances and deductibles due on any tests and/or procedures that are required and

[redacted]

considered standard care.

Trigriluzole is provided at no cost to you by the study sponsor.

If you participate in the optional biopsies, there will be no cost to you for the biopsy.

If you have any questions about insurance coverage, including any out of pocket expenses you might incur, or which laboratory or facilities you are allowed to have tests at, a financial counselor will be made available to you upon request.

Will you be paid to take part in this study?
You will not be paid for your participation in this research study.

How will information about you be kept private or confidential?
All efforts will be made to keep your personal information in your research record confidential, but total confidentiality cannot be guaranteed.

Your personal health information, identifiers and research data are stored and kept in a secure area in the [redacted]. Computer screens containing personal health identifiers are inaccessible to public view. Only the study doctor and research team will have direct access.

A description of this clinical trial will be available on ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this website at any time.

What will happen if you are injured during this study?
If you take part in this study, you will be exposed to certain risks of personal injury in addition to those associated with standard forms of treatment.

In addition, it is possible that during the course of this study, new adverse effects of trigriluzole that result in personal injury may be discovered. Please refer to section 'What are the risks and/or discomforts you might experience if you take part in this study?"

The University will make appropriate referrals for medical and/or dental treatment for subjects who sustain personal injuries or illnesses as a direct consequence of participation in the research. The subject's health insurance carrier or other third-party payer will be billed for the cost of this treatment; provided that the University shall not submit to federally funded programs, e.g., Medicare, Medicaid or CHAMPUS, for reimbursement first if submission to such programs is prohibited by law. No financial compensation will be provided by the University and no other type of assistance is available from the University.

What will happen if you do not wish to take part in the study or if you later decide not to stay in the study?
Participation in this study is voluntary. You may choose not to participate or you may change your mind

at any time.

If you do not want to enter the study or decide to stop participating, your relationship with the study staff will not change, and you may do so without penalty and without loss of benefits to which you are otherwise entitled.

You may also withdraw your consent for the use of your data, but you must do this in writing to [redacted] (address provided on page 1).

Any data that has already been sent to the sponsor, the Office of Human Research Services at the [redacted] cannot be withdrawn because there may not be any identifiers to link the data with you. We are required by the Food and Drug Administration however, to continue to report anything that relates to the safety of these drugs.

At any time, the study doctor can take you out of this study because it would not be in your best interest to stay in it. Your study doctor can stop treatment even if you are willing to stay in the study.

If you decide to withdraw from the study for any reason, you may be asked to return for at least one additional visit for safety reasons.

Also, you should understand that the sponsor, in consultation with the study doctor, can withdraw you from the study at any time if you do not follow the instructions related to the study, if you need a different treatment, or if you have a study-related injury.

Who can you call if you have any questions?
If you have any questions about taking part in this study or if you feel you may have suffered a research related injury, you can call the study doctor:

[redacted]

If you have any questions about your rights as a research subject, you can call:

[redacted]

What are your rights if you decide to take part in this research study?
You have the right to ask questions about any part of the study at any time. You should not sign this form unless you have had a chance to ask questions and have been given answers to all of your questions.

PERMISSION (Authorization) TO USE OR SHARE HEALTH INFORMATION THAT IDENTIFIES YOU FOR A RESEARCH STUDY

Information about you and your health is personal and private, so this information generally cannot be used in research without your written permission. The next few paragraphs tell you about how researchers want to use and share your health information in this research study. Your information will only be used as described here or as allowed or required by law. Ask questions if you do not understand any part of the research or the use of your health information. If you sign this consent form, you agree to let the researchers use your information in the research and share it with others as described below.

What is the purpose of the research and how will my information be used?
You are being invited to take part in this research study which is described at the beginning of this form. The purpose of collecting and using your health information for this study is to help researchers answer the questions that are being asked in the research.

What information about me will be used?

- All information in your medical record
- Hospital discharge summaries
- Radiology records or images (MRI, CT, PET scans)
- Medical history or treatment
- Medications
- Consultations
- Laboratory/diagnostic tests or imaging
- EKG and/or EEG reports
- Pathology reports, specimen(s) or slide(s)
- Emergency Medicine reports

Who may use, share or receive my information?
The research team may use or share your information collected or created for this study with the following people and institutions:

- [redacted]

Those persons or organizations that receive your information may not be required by Federal privacy laws to protect it and may share your information with others without your permission, if permitted by the laws governing them.

Will I be able to review my research record while the research is ongoing?
No. We are not able to share information in the research records with you until the study is over. To ask for this information, please contact the Principal Investigator, the person in charge of this research study.

Do I have to give my permission?
No. You do not have to permit use of your information. But, if you do not give permission, you cannot take part in this research study. (Saying no does not stop you from getting medical care or other benefits you are eligible for outside of this study.)

If I say yes now, can I change my mind and take away my permission later?
Yes. You may change your mind and not allow the continued use of your information (and to stop taking part in the study) at any time. If you take away permission, your information will no longer be used or shared in the study, but we will not be able to take back information that has already been used or shared with others. If you say yes now but change your mind later for use of your information in the research, you must write to the researcher and tell him or her of your decision:

[redacted]

How long will my permission last?
There is no set date at which your authorization will expire. This is because the information used and created during the study may be analyzed for many years, and it is not possible to know when this will be complete.

Where can you get more information?
You may call the National Cancer Institute's Cancer Information Service at:
Voice: 1-800-4-CANCER (1-800-422-6237)

You may also visit the NCI Web site at http://cancer.gov/
For NCI's clinical trials information, go to: http://cancer.gov/clinicaltrials/
For NCI's general information about cancer, go to http://cancer.gov/cancerinfo/

If you do not have access to a personal computer, you may access these websites and other information at a computer in the Resource and Learning Center on the second floor of the Cancer Institute of New Jersey at no cost to you.

Consent for optional biopsy(ies):
I consent to 1-3 biopsy procedures for biological sampling of my tumor, which I will donate for the purposes of scientific research, and according to the option(s) I have initialed/signed below:

I agree to donate an additional tumor sample taken at disease recurrence to be used for additional research related to my cancer and/or its treatment:	☐ Yes	☐ No	_____ Initials of Patient

AGREEMENT TO PARTICIPATE
I have read this entire form, or it has been read to me, and I believe that I understand what has been discussed. All of my questions about this form or this study have been answered.

I agree to take part in this study.

Subject Name:_____

Subject Signature:_____ Date:_____

Signature of Investigator/Individual Obtaining Consent:
To the best of your ability, you have explained and discussed the full contents of the study including all of the information contained in this consent form. All questions of the research subject and those of his/her parent or legal guardian have been accurately answered.

Investigator/Person Obtaining Consent:_____

Signature:_____ Date: _____

[redacted]
Version date: 12/04/2018

[redacted]

Expiration Date: 4/3/2020

FOR NON-ENGLISH SPEAKING SUBJECTS:

Signature of Reader/Translator If the Subject Does Not Read English Well:

The person who has signed above, _____, does not read English well. You read English well and are fluent in _____ (*name of the language)*, a language that the subject (his/her parent(s)/legal guardian) understands well. You understand the content of this consent form and you have translated for the subject (his/her parent(s)/legal guardian) the entire content of this form. To the best of your knowledge, the subject (his/her parent(s)/legal guardian) understands the content of this form and has had an opportunity to ask questions regarding the consent form and the study, and these questions have been answered (his/her parent(s)/legal guardian).

Reader/Translator Name:_____

Reader/Translator Signature:_____ Date:_____

Witness Name:_____

Witness Signature:_____ Date:_____

[redacted]
Expiration Date: 4/3/2020